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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/037,243	01/04/2002	Paul I. Freimuth	BSA 01-22	6646
26302 7590 01/09/2008 BROOKHAVEN SCIENCE ASSOCIATES/ BROOKHAVEN NATIONAL LABORATORY BLDG. 185 - P.O. BOX 5000 UPTON, NY 11973			EXAMINER MITCHELL, LAURA MCGILLEM	
			ART UNIT 1636	PAPER NUMBER
			NOTIFICATION DATE 01/09/2008	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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**Advisory Action
Before the Filing of an Appeal Brief**

Application No.

10/037,243

Applicant(s)

FREIMUTH ET AL.

Examiner

Laura M. Mitchell

Art Unit

1636

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 28 November 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
(a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
(b) ☒ They raise the issue of new matter (see NOTE below);
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: See Continuation Sheet. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
The status of the claim(s) is (or will be) as follows:
Claim(s) allowed: _____.
Claim(s) objected to: _____.
Claim(s) rejected: 64, 99 and 100.
Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____.
13. ☒ Other: See Continuation Sheet.

Joe W. Foster
AU1636

CONTINUATION SHEET

3. It is noted that claim 64 and 99 have been amended to recite the phrase "A pET-type expression vector" or "A pET-type *E.coli* expression vector". The instant specification does not provide a limiting definition of "pET-type vector". Therefore, the phrase "pET-type" can be broadly interpreted to mean any vector that is similar to a pET vector. Therefore, the claims encompass a large genus of vector that would encompass a "pET-type vector". The instant specification does not provide support a genus of vectors that are pET-type. Therefore, this claim amendment constitutes impermissible new matter. In addition, the amendments to claim 64 and 99 change the scope of the claimed vector so that an additional search would be required for pET-type vectors with the claimed limitations.

11. Once a final rejection that is not premature has been entered in an application, applicant or patent owner no longer has any right to unrestricted further prosecution. The amendments do not place the application either in condition for allowance or in better form for appeal. For reasons given above, and on the grounds that the amended claims potentially include new matter and raise further issues for consideration which would require an additional search of the prior art, the amended claims have not been entered. The amendments do not place the application either in condition for allowance or in better form for appeal. Applicant is invited to review MPEP 714.12.

13. Claims 64 and 99-100 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is being maintained for reasons of record in the previous Office Action, mailed 5/5/2006 and for reasons outlined below.

Applicants submit that to limit the claim to address only proteins or polypeptides requiring enhancement of folding and solubility would be irrelevant to the notion of "enhancement". Applicants submit that it is well known that many proteins when expressed in *E. coli* may fold properly and be soluble when expressed under a given condition (such as a particular temperature), but may require enhancement of folding and solubility when expressed under other temperature conditions. Applicants submit that in such a circumstance, one could use the peptide extension vectors in either or both expression conditions where the peptide would play a prominent role in one (e.g., 37°C) and a minor or no role, in the other condition (37°C). In addition, Applicants submit that **enhancing** the solubility and folding of a protein or polypeptide of interest may or may not be solely applicable to a protein or polypeptide in need of such enhancement. It could be a more subtle "enhancement". Therefore, the Agent submits that this requirement should be at best a "conditional" requirement and that the invention is not solely limited to use with proteins that absolutely require such enhancement. The Agent therefore submits that to require the use of the peptide

extension expression vectors solely for proteins that wouldn't ordinarily fold properly or be soluble is not relevant.

The amended Claim 64, being drawn to a pET-type vector for use in *E. coli*, having any one of the claimed peptide extensions for production of fusion proteins is fully disclosed in the written description. One of skill in the art would immediately recognize that other pET vectors could be used in place of pET15, the peptide extensions could be readily substituted one for the other as in the examples in the Specification, and the protein or polypeptide of interest is commonly replaced in such expression vectors, depending upon one's interest in a particular protein or polypeptide. Applicants submit that it would be a very strange world if all scientists studied the same recombinantly expressed protein or polypeptide.

In addition, to address the remarks on pages 6 to 7, the Agent respectfully submits that through the written description, which includes the examples of ClpX (for which T7B and other variants of T7B were fused to enhance its solubility and folding) and various yeast proteins (pages 36 - 37), those of skill in the art would know how to replace the peptide extension T7B with the others claimed and how to replace the protein or polypeptide of interest in all vectors, including all pET-type vectors. Thus, the written description would be readily interpreted by one of ordinary skill to encompass pET-type expression vectors encoding any of the claimed peptide extensions and any protein or polypeptide of interest. They do not need to be instructed as to "how the structure of vector pET15 comprising CAR D1 T7B relates to the

structure of the claimed expression vector". It is clear to those of skill, particularly as the presently amended claims are limited to pET-type expression vectors.

In addition, the Agent respectfully draws the Examiner's attention to the "Synopsis of Application of Written Description Guidelines" - "... the examiner has the initial burden, after a thorough reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claim. Clear evidence or reasons do not appear to be present in the Office Action. Amended claims 64 and 99 are directed to pET-type vectors for expression in *E. coli*, of which the fully exemplified pET15 is a representative type. Applicants submit that many pET-type vectors are well known to those of skill in the art, while pET15 was prominently used in the Examples as a representative of the genus of pET-type vectors. Those of ordinary skill in the art who would read this specification would know that other pET vectors could be used interchangeably for pET15.

Applicant's arguments filed 11/28/2007 have been fully considered but they are not persuasive. Applicants submit arguments regarding the claim limitation of a vector comprising proteins or polypeptides requiring enhancement of folding and solubility. The claims are drawn to particular vectors comprising gene encoding protein or a polypeptide of interest, which requires that the gene encoding protein or a polypeptide of interest be present in the vector. The proteins and polypeptides of interest are present in the vector for enhancement of the solubility and proper folding. Regardless of how subtle or conditional the need for enhancement of solubility or

folding may be, the protein or polypeptide of interest would require it, in order for the gene to be present on the vector. The vector as claimed does not merely include a cloning site for a sequence encoding a protein or polypeptide of interest, but rather includes the sequence encoding a protein or polypeptide of interest. Therefore the claimed vector encodes a very large genus of any sequence encoding a protein or polypeptide which has not been sufficiently described in the instant specification. The specification has not provided a sufficient description of the structure of proteins that would correlate with any need for enhanced folding or solubility, either subtle or conditional.

Although the skilled artisan would know how to replace a sequence encoding a protein or polypeptide of interest in a pET vector for the purpose of making a fusion protein to enhance folding, the skilled artisan would not know what sequence encoding a protein or polypeptide of interest to place in the vector that would still meet the limitations of the claimed vector, from the information provided in the specification.

It is noted that claim 64 has been amended to remove the phrase "for enhancing the solubility and proper folding of a protein or polypeptide of interest". However, this is the disclosed function for the claimed expression vector. Furthermore, the specification does not provide a limiting definition of "pET-type vector". Therefore, the phrase "pET-type" can be broadly interpreted to mean any vector that is similar to a pET vector. Therefore, the claims encompass a large genus of vector that would encompass a "pET-type vector". The instant specification does not provide support a genus of vectors that are pET-type so that the structure of a pET vector is correlated with the function of

a pET vector. The specification does not describe the structural elements that qualify a vector as a "pET-type" vector so that it would function as a pET vector.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura M. Mitchell whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura McGillem Mitchell
Examiner
12/10/2007